Nucleophilic Substitutions of 6I-O-Monotosyl-β-cyclodextrin in a Planetary Ball Mill

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ABSTRACT. The tosyl group (Ts) on 6^{I}-*O*-(*p*-toluenesulfonyl)-β-cyclodextrin has been substituted with halogenides, nitrogen and sulfur nucleophiles under mechanochemical conditions and the reaction has been investigated in this work. The preparation of mono-substituted cyclodextrin (CD) derivatives, such as azido-, thioureido-, iodo- and thioethers, is shown to be more advantageous in a planetary ball mill (BM) than classic solution methods. All BM reactions

displayed poor salt cation dependency, but a considerably stronger anion nucleophilicity effect has been observed. Although CD monoderivative syntheses were performed on a hundred milligram scale, the scalability of the method has been investigated and supported by the preparation of 6^{I}-monoazido-6^{I}-monodeoxy-β-CD.

INTRODUCTION

Grinding is the simplest and one of the oldest methods for the preparation of physical mixtures of various powders. Ball milling (BM) is the most effective method to grind materials into extremely fine powders for use in mineral dressing processes, paints, pharmaceutics, pyrotechnics, etc. as documented in several books.[1-3] Conventional ball mills consist of a cylindrical or conical shell which rotates on a horizontal axis and a grinding medium of steel, flint or porcelain balls. BM brings several advantages over other systems: the costs of installation, power and the grinding medium are low; it is suitable for both batch and continuous operation; while being similarly suitable for both open and closed circuit grinding as well as being applicable for materials of all degrees of hardness.

Aside from common ball mills, there is a second generation, often called High-Speed Ball Mills (HSBM), which operate in vibrating, mixer or planetary mode. The simplest and oldest vibrating ball mill, which consists of a small milling cup with one or two balls, is commonly used in sample homogenization for infrared (IR) spectroscopy. A planetary ball mill consists of at least one grinding jar which is arranged eccentrically on a so-called sun. The difference in speeds between the balls and grinding jars produces an interaction between frictional and impact forces, which releases high dynamic energies. The interplay between these forces results in a high and very effective degree of size reduction in a planetary ball mill.[1-3] Detailed descriptions of operating

modes and theoretical considerations can be found and well discussed in various product brochures.

High-energy ball milling (HEBM) is a simple, effective technique with which to produce various nanocrystal powders in high-energy planetary and vibratory mills and is usually used as a synonym for HSBM. The principles of its running are the same as for conventional BM techniques; the higher the intensity and duration of grinding and the smaller the weight and size of particles of source powder to be milled, the smaller the average size of the powder particles produced. The finest grinding is achieved by wet technologies, using a liquid milling medium (alcohol or other organic solvents).[4] The high speed attained by the ball bearing provides enough force to turn the reagents into an amorphous mixture, which subsequently facilitates chemical reactions.

Cyclodextrins (CDs) are natural cyclic glucose derivatives which are able to form, via non-covalent interactions, so-called inclusion complexes which improve the solubility, bioavailability, chemical stability, etc., of guest molecules. These oligosaccharides consist of $\alpha(1\rightarrow4)$ linked glucopyranoside units whose cyclic structure creates a truncated cone-shape where the primary hydroxyls of the glucose units are on the narrower and the C(2) and C(3) hydroxyls are on the wider edge. The secondary hydroxyl groups give strong hydrophilic character to the secondary hydroxyl rim which influences the reactivity of these hydroxyls. The most commonly used natural CDs have 6-, 7-, and 8 glucopyranoside units and, while higher membered versions, of up to 150 units, also exist, they are important from a scientific rather than practical point of view as their complex forming ability is lower than that of the more common CDs.[5,6]

The preparation of CD and other complexes with the aid of BM is also well known.[7,8] The scale-up of this technology is easy and is used for the production of several drugs (e.g. steroids,[9] sulfonamides,[10,11] and macrolide antibiotics,[12] etc.) with solid CDs. A potential drawback of this

technology is that it may give metastable crystalline complexes which can recrystallize upon storage to reach an equilibrium state (e.g. β-CD complexes of diazepam, indomethacin, warfarin, hydrocortisone acetate).[13] Another serious drawback of BM, particularly of the high energy version, is the degradation of mill surfaces and subsequent suspension contamination.[14]

CD derivatives which bear a good leaving group, such as arylsulfonylated or halogenated CDs, are important intermediates in CD functionalization. Regioselective substitutions can be achieved effectively with aromatic sulfonyl reagents and the formed derivatives are able to form intra- and intermolecular complexes with their pendant groups. These activated derivatives are poorly soluble in water and their substitution reactions often require high boiling point dipolar aprotic solvents, such as DMF, DMA, DMSO, NMP, or HMPT. The complete removal of these solvents is obviously difficult and so the prepared compounds require further purification steps. Additionally, these solvents are environmentally unfavorable due to their decomposition during storage/reactions, while their persistency and toxicology profile are also problems. In environmentally benign methods, the best solvent is the "no solvent". The introduction of real solventless technologies into CD derivatization opens up new and efficient paths in CD derivatization. During the finalization of this manuscript, an efficient HEBM method for 2-monotosylated CDs and their conversion to internal ethers, mannoepoxides, was described in a recent publication by Menuel *et al.*[15]

Although the preparation of complexes and microparticles with ball milling is common, its use in organic chemical reactions is still a peculiarity rather than everyday practice. While we can find many inorganic reactions and their potential industrial uses in literature,[2] organic chemistry, particularly the carbohydrate field, is less popular.

Nucleophilic substitution reactions are important components of organic syntheses. Many of these reactions frequently involve an apolar organic compound and a polar ionic salt. These reactions are partly heterogeneous because the reagents are poorly soluble in a single solvent system and may show strong solvent dependency. Polar aprotic solvents are preferred for use in SN2 reactions, although they are not vital to the success of the reaction. The SN2 reaction can still occur without solvent stabilization because a charged species is not formed in the transition state.[16] The other type of nucleophilic reaction, the SN1 reaction, is a unimolecular nucleophilic substitution. The transition state of the SN1 reaction mechanism resembles an ion-pair, much like the intermediate, as opposed to resembling the reactants, as seen in the SN2 transition state.[17] Solvent effects are critical to the mechanism of the SN1 reaction. Solvent interactions with the reactants, transition state, intermediate species and products can affect the free energy of each state which, in turn, affects the ease at which the reaction goes to completion. Protic solvents promote leaving group dissociation by stabilizing the leaving group, while polar solvents promote bond heterolysis by stabilizing the carbocation intermediate relative to the covalently bonded starting material.[18]

Although polar aprotic solvents, such as DMF or HMPT, can occasionally solve the problem of heterogeneity, solvent removal is accompanied by increasing costs and high environmental impact, particularly in kilolab-scale syntheses. Phase transfer catalysts (PTC) are good alternatives in these reactions, but are usually expensive for industrial processes, thus limiting their use, despite resulting in higher product yields which may pay for the extra cost, despite purification being troublesome. An additional drawback of PTC is the use of non-environmentally friendly solvents, like halogenated hydrocarbons or ethers. Cyclodextrins can also be used as PTC, but this entails more structural and reaction restrictions which are considerable limiting factors.[19-21]

Groups such as tosylate, triflate and mesylate can delocalize the acquired negative charge and are thus considered non-nucleophilic; they will not compete with the nucleophilic reaction by attempting to re-form the starting material. The basic principles of both SN1 and SN2 reactions are thoroughly discussed in organic chemistry textbooks.

Although polar aprotic solvents, such as DMF or HMPT, can occasionally solve the problem of heterogeneity, solvent removal is accompanied by increasing costs and high environmental impact, particularly in kilolab-scale syntheses. Phase transfer catalysts (PTC) are good alternatives in these reactions, but are usually expensive for industrial processes, thus limiting their use, despite resulting in higher product yields which may pay for the extra cost, despite purification being troublesome. An additional drawback of PTC is the use of non-environmentally friendly solvents, like halogenated hydrocarbons or ethers. Cyclodextrins can also be used as PTC, but this entails more structural and reaction restrictions which are considerable limiting factors.[19-21]

Solvent-free reactions avoid the negative effects of solvents at the cost of foregoing the positive effects, as demonstrated by Braun *et al.* in the preparation of fullerene derivatives by mechanochemical activation with the aid of γ-CD. BM is a process that allows solids to mix in the absence of a solvent and perform the reactions under less polluting conditions.[22]

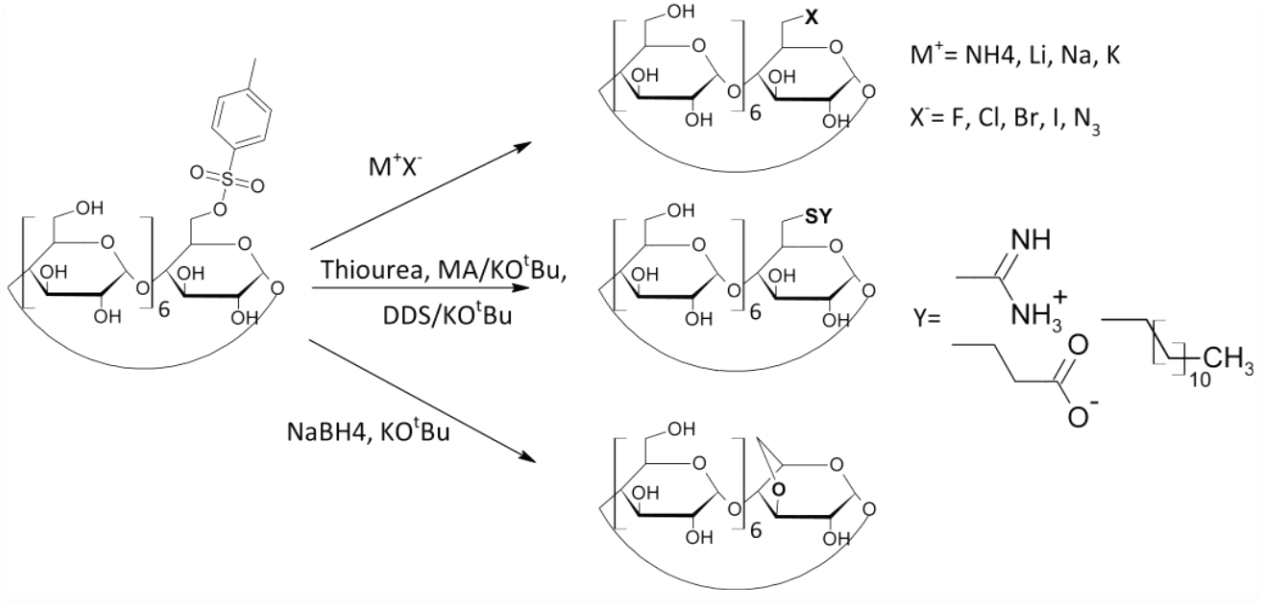
While solid state intermolecular SN2 reactions only depend on the contact between interacting particles, SNi reactions may show more structure dependent behavior, as their solid state structures can be either favorable or unfavorable.

Despite the fact that BM reactions are usually stated as being solvent free methods in many cases, particularly when the mass ratio of the reagents is very high, some – from the reaction viewpoint - inert solvents can be applied. The literature may suggest that a lack of solvent in BM conditions favors the SN2-type reaction, but it is also true that the solventless environment does

not necessarily mean that there is a lack of a liquid phase. It is also worth noting that one or two of the reaction mixture reagents may occasionally be liquid and serve as a solvent, thus meaning that solvent effects and the SN1-type reaction cannot be excluded. A good example of a mixed reaction mechanism is glycosylation, where not only the solvent properties determine stereochemistry by stabilizing transition state geometry, but, in many cases, the reaction consists of two steps where the armed glycoside is first ionized by a promoter and the stability of the formed cation, reactivity and steric relationships determines the final outcome of the reaction. In the classic Koenigs-Knorr glycosylation by Tyagi *et al*,[23] SN2 glycosylation seems to be dominant, without neighboring group participation. However, no comparison with the real solution reaction is described. Better confirmation of a pure SN2 reaction is provided by Patil and Karta[24] and thioglycosides yields are close to being quantitative. Unfortunately, reaction mixture composition information is missing in both cases and chromatographic purification and recrystallization have an effect on the enantiomeric ratio of the isolated products.

The present paper deals with the reactions of anions of various inorganic salts and tosylated β-CD in HEBM conditions. The exchange of the primary tosyl ester with various anions is normally a routine process both in organic chemistry and CD derivatization. Although, only a few anions have real practical importance, the exchange rate is an important factor in an *a priori* estimation of yields. While the Ts group itself is a good leaving group, it is often changed to bromide or iodide in order to improve solubility and simplify the work-up in CD derivatizations. Even more emphasis is being given to a green synthetic method for the bulk production of important intermediate, the azido CD derivatives,[25] or CD thiols and thioethers of favourable aggregation properties in nanomedicines, and particularly the antidote Sugammadex.[26] The preparation of fluorinated CDs, particularly the 6-monofluoro version is rather challenging, however the special structure of CDs

can give important information not only as to the substitution ability of the fluoride ion, but also to the effect of complexation of various halogenide salts, as well. In order to avoid configuration changes in the reactions, a primary rim activated derivative, 6^I-O-monotosyl-β-CD (TsβCD), was chosen to study the nucleophilic replacement reactions. The effectiveness of our method for the synthesis of an important CD intermediate, 6^I-monoazido-6^I-monodeoxy-β-CD, has been demonstrated in a gram-scale preparation. A lack of polar aprotic solvent reactive impurities resulted in a more effective preparation of sulphur containing CD derivatives from thiourea (TU) and mercaptopropionic acid (MA), as demonstrated here for 6^I-monodeoxy-6^I-S-monothioureido- and 6^I-monodeoxy-6^I-S-mono(3-mercaptopropionyl)-β-CDs.



Scheme 1. Nucleophil substitution reactions of TsβCD using HEBM method

EXPERIMENTAL

Ball mill: Retsch PM100 High Speed Planetary Ball Mill, 1500 steel balls of 1 mm diameter and 50 steel balls of 5 mm diameter (m=70.5 g, V=15 ml), 650 min-1 for 60 min, weight = 780 g (jar, cap, and balls).

TsβCD was prepared according to literature.[27] Reagents and solvents were purchased from Alfa Aesar and Sigma Aldrich. The activated strong ion exchangers were washed with water and then with MeOH until they were neutral and colorless and dried overnight at room temperature. The dry ion exchangers were stored in a deep freezer.

TLC: Merck 5554 Silicagel 60. Runs: saturated chamber at 7 cm, using 10:7 (v/v) dioxane cc. aq. NH_3. Visualization: UV 254 nm and charring at 100-110 °C after spraying with 15 % cc. sulfuric acid in abs ethanol. R_F values.

TsβCD	0.38-0.43	6-Br-β-CD	0.30-0.33
$3^I,6^I$-mono-β-CD	0.24-0.28	6-I-β-CD	0.32-0.35
β-CD	0.20-0.24	6-N_3-β-CD	0.34-0.37
6-F-β-CD	0.26-0.29	6-MPA-β-CD	0.26-0.29
6-Cl-β-CD	0.29-0.32	6-DDS-β-CD	0.53-0.56
TsOH	0.57-0.62		

HPLC: Waters system (pump: 1525, UV: 2998, ELSD: 2424), using XTerra® C18 column (4.6*150 mm, 5 μm) at 23 ± 1 °C. Eluent: 0.1% TFA/water-acetonitrile (gradient: 5 % → 50 %).

NMR spectra were recorded on a Bruker Avance 300 MHz. Solvent residuals were used as internal standards.

Thermometer: Lafayette TRI-88 no-contact thermometer, built-in laser pointer, with ± 2 °C reading accuracy, 8:1 distance to spot size, at 18-23 cm measuring distance.

Solution reactions.

a) 6^{I}-Monoazido-6^{I}-monodeoxy-β-CD[21]

TsβCD was reacted in abs. DMF (c~ 20 %) at 105-110 ºC with sodium azide (20 % molar excess). DMF was evaporated and the residue was crystallized under acetone. The crude products were recrystallized from water with acetone precipitation.

	Yield	
Scale [mol]	m [g]	%
0.050	57.0	98
0.003	3.1	89
0.001	0.9	78

b) 6^{I}-Monodeoxy-6^{I}-monothiouronium-β-CD tosylate[28]

TsβCD (0.5 g, 0.00038 m) was reacted in DMF (4 mL) with thiourea (0.3 g, 0.038 m) at 140 °C using 20 min of MW irradiation. The crude product was isolated in the same way as the monoazido-β-CD. Yield: 0.37g, 73 %.

General procedure for high energy ball milling reactions

a) *Benzyl iodide*

Benzyl bromide (0.34 g, 0.002 mol) and sodium/potassium iodide (0.006 mol) were weighed directly into the balls jar. The suspension was ball milled for 35 (NaI) and 30 (KI) mins at maximum speed (650 min^{-1}). The outer temperature stayed below 45 °C in both experiments, while the inner temperatures were around 45 °C at the end of the milling process. The jar was cooled to

room temperature and the liquid phase was removed and then diluted with diisopropyl ether (10 mL). GC-MS analysis showed benzyl bromide (13.10 min) and iodide (16.04 min) peaks.

	BnBr (13.10 min)	BnI (16.04 min)
NaI	23.4 %	76.6 %
KI	13.2 %	86.8 %

b) *Halogenides, azides and thiourea*

Air-dry TsβCD (0.0001 mol) and the salts (0.0003 mol) were mixed with a spatula in the ball mill prior to being ball milled for 60 min. Mass ratio of the reagents/balls are varied from ~520 to ~390. The temperature was checked after 30 and 60 min using the infra thermometer.

c) *Thiols*

Dry conditions: Air-dry TsβCD (0.13 g, 0.0001 mol), the thiol (0.0003 mol), and potassium t-butoxide (0.0003 mol for 1-dodecanethiol and 0.0006 mol for 3-mercaptopropionic acid) were mixed and then ball milled. Mass ratio of the reagents/balls are varied from ~370 to ~190. The temperature was checked after 30 and 60 min using an infra thermometer.

Wet conditions: The thiol (0.0003 mol) was mixed with 1-pentanol (30 μL), and then potassium t- butoxide (0.0003 mol for 1-dodecanethiol and 0.0006 mol for 3-mercaptopropionic acid) was added. The solid formed was cracked with a spatula and air-dry TsβCD (0.0001 mol) was added and ball milled for 60 min. The temperature was checked after 30 and 60 min using an infra thermometer.

Work-up methods:

b1) *Halogenides and azide.* The ball milled solid was dissolved and the balls were washed in 50 % EtOH (30 mL), and then removed. The solution was then treated with ion exchangers. After

the ion exchangers were removed, the neutral solutions were clarified with charcoal and solvents eliminated by evaporation. 0.05-0.09 g of solids were obtained.

b2) *Thiourea.* The ball milled solid was washed with abs. EtOH and the solid residue was dissolved after drying in water and clarified with charcoal. The solid materials were obtained by freeze-drying. The solid was recrystallized from aqueous acetone. Yield: 0.10 g, 73 %

c1) *Mercaptopropionic acid*. The ball milled solid was dissolved in water, stirred with strong ion exchangers (0.6-0.6 mmol) for an hour, then with charcoal (0.2 g) for an additional 30 min, filtered and the water was removed by freeze-drying. Dry condition yields: 0.06 g (~48 %); wet: 0.08 g (~64 %).

c2) *Dodecanethiol.* The ball milled solid was suspended in water and filtered. The residue was then dissolved in MeOH, insolubles were removed by filtration and the solid product was obtained by evaporation. Dry condition yield: 0.03 g (~23 %); wet conditions: 0.09 g (~68 %).

Preparative scale synthesis of 6^I-monoazido-6^I-monodeoxy-β-CD

The equipment was the same as used for the small scale experiments. Air-dry TsβCD and sodium azide (3 molar equiv) were mixed with a spatula in the ball mill and milled for 60 min (0.0001 and 0.0025 mol) or 90 min (0.005 mol). The solid was separated from the balls by sieving (except the 0.0001 reaction when the work-up was as described in work-up b1), the jar and the balls were washed with water, the insolubles were filtered through a charcoal bed and identified as a mixture of the product and the starting TsβCD and discarded. Water was removed from the clear solution by freeze-drying.[26] The sieved and freeze-dried solids were combined and recrystallized from the water-acetone system as described previously. Yields are 69-90 %, see Table 3. The product showed an identical NMR spectrum to that of the sample prepared by the classical method.[30]

Yield

Scale [mol]	m [g]	%
0.0050	5.2	90
0.0025	1.6	62
0.0001	0.08	69

RESULTS AND DISCUSSION

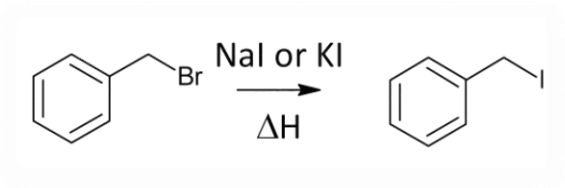
Internal temperature measurements presented difficulties across all experiments. Despite attempts at rationalization and standardization, relative large variability (3-5 °C) was found in internal temperatures. A "measurement matrix" was therefore created, which took the form of a five on a die, two measurements were made at each point and the values were then averaged. The calculated standard deviations were around the reading accuracy. The temperature variation of the outer side of jar was significantly smaller. The largest deviation was found on the cap of the reaction vessel.

System suitability test.

The Finkelstein-reaction is a classic example of an SN2 reaction involving halogen exchange (Scheme 2). The first experiments carried out this type of nucleophilic substitution reaction in a HSBM without the use of solvent.[31] Literature methods usually used vibrating ball mills in high energy ball milling synthetic transformations.

Both sodium and potassium iodide were used in experiments to check our planetary ball mill equipment for the model reaction and GC-MS analysis only showed benzyl bromide (13.10 min) and iodide (16.04 min) peaks after ball milling. During the ball milling, the temperature of the jar remained below 45 °C, and at the end of the experiments, the internal temperature was around 50 °C. Mass ratios of the reagents/balls were ~57 (NaI) and ~53 (KI) in these experiments. Under these non-optimized conditions the yields were acceptable: 77 % (NaI, 40 min HEBM) and 87 %

(KI, 35 min HEBM) analytical yields. These results are comparable or better than mixer or vibrating methods, where similar reactions of 4-bromobenzyl bromide resulted in product yields of 94 % (NaI) and 58 % (KI) (1 hr, mixer mode),[2] or 53 % (KI, 16 hrs, vibrating mode).[32] GC-MS chromatograms are in the SI as Fig. S1 and S2.



Scheme 2. The Finkelstein-reaction

Behavior of TsβCD.

Various amounts of starting material alone were ball milled for 90 min - the maximum reaction time used in our experiments - and the internal and external temperatures of the jar were registered. The outer temperature of the jar showed a saturation-type curve around 40-45 °C after 15-20 min in all cases, independently of its content. A slightly lower temperature (35-40 °C) was measured in wet conditions. Internal temperatures showed larger deviations, as it is seen in Figure 1; the temperature maximum was approximately identical to the outside temperature in the absence of a starting material, while the temperature rose to approx. 80 °C when TsβCD was added and milled with the higher weighed amount resulting in a somewhat lower final value, as seen in Figure 5. Using n-pentanol (1-PeOH) as the wetting medium gave a sigmoid type temperature vs. time curve. Mass ratio of the reagents/balls was varied from 0 to ~160 in these experiments. Thin layer chromatography (TLC) of the ball milled samples did not show decomposition products, such as β-CD (hydrolysis) and 3,6-monoanhydo-β-CD (intramolecular reaction).

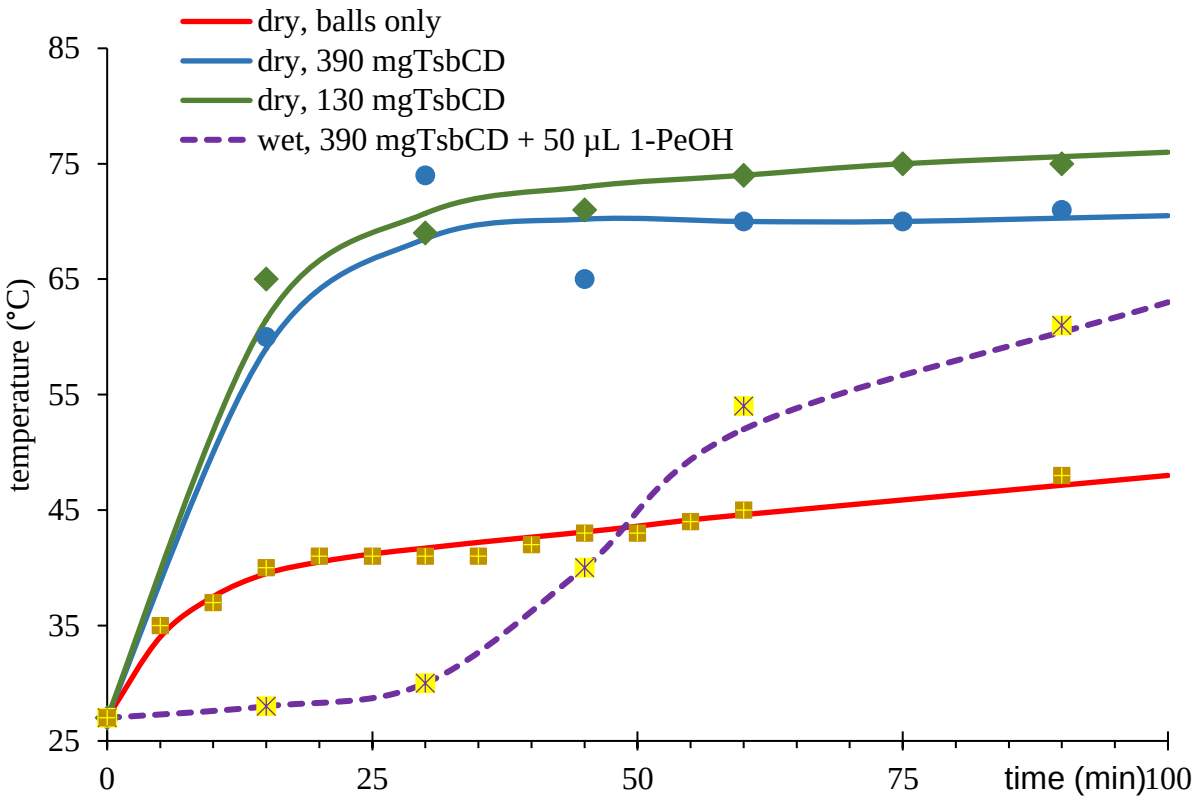


Figure 1. Temperature profile during high energy ball milling of TsβCD without reagents.

It is known that TsβCD can be hydrolyzed under mild conditions and that the formation of 3,6-monoanhydro-β-CD is unavoidable in presence of a base.[33] It was found that air-dried TsβCD (as it is stored in a bottle after purification) contains 3-5 % water. The effect of CD water content on HEBM condition reactions has been shown in a very recent publication by Menuel,[15] although the residual water content of TsβCD is considerably lower than that of naked CDs. In order to observe the possibility of complete drying and to optimize drying conditions, the water content of the prepared TsβCD was investigated on a 10 g scale and at higher temperatures (65 and 80 °C) on a 1 g scale after no further weight loss was found at 40 °C for 3 days. Chemical integrity was checked by TLC. It was found that higher temperature drying not only gave water loss together with some decomposition, indicated by yellow coloration, while increasing amounts of β-CD and $3^{I},6^{I}$-

monoanhydro-β-CD, but it was also seen that the dried product re-adsorbed water from air relatively quickly at room temperature, as seen in Figure 2 (right scale). Finally, optimal conditions for drying were found to be 40 °C in a vacuum (150-200 mbar) in the presence of KOH and P_2O_5. The prepared TsβCD was dried to constant weight, as seen in Figure 2 (left scale) and stored in a normal glass container. The weight of the dried material did not change over a one-month period. The dried sample still contained approximately 5 % water, as determined by Karl-Fisher titration.

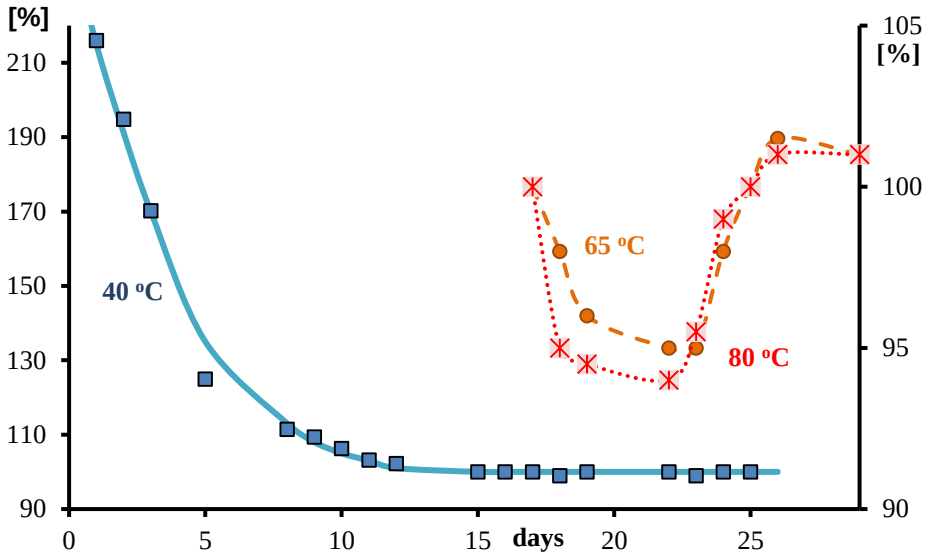


Figure 2. Drying of TsβCD (left scale 40 °C, right scale 65 and 80 °C). Values are relative to the constant weights.

In basic solution, the molecular motions of the glucopyranose unit readily allow the formation of the $3^I,6^I$-monoanhydro-glucopyranose unit usually together with the hydrolytic byproduct, unsubstituted β-CD. Hydrolysis may be suppressed in the solid state because water molecules can preferably locate close to the more hydrophilic parts of the CD. Unfortunately, no single crystal diffraction data is yet available for TsβCD despite its easy crystallization. When using potassium *t*-butoxide as the reagent, $3^I,6^I$-monoanhydro-β-CD is almost the only product from TsβCD and

conversion is almost quantitative, as can be seen in Figure 3 and Table 2. Using a less basic reagent, sodium borohydride, also principally gave 3^{I},6^{I}-monoanhydro-β-CD, although conversion was lower and more than one product was formed.

Proof of concept. BM without additional base.

The measured thermal effects are summarized in Tables 1a and b. As expected and seen in the tables, there is practically no relationship between internal and external temperatures. The high weight ratio between the jar + balls and reactants – generally around 200:1 - does not allow considerable warming of the equipment to occur over the no-reaction temperature. However, it is surprising to see that energy transfer was slow between the balls and jar despite reaction heat being transferred from the metal balls to metal jar.

Table 1a. Measured average temperatures inside the jar at the end of BM (after 60 min, rounded)

M\X	F^-	Cl^-	Br^-	I^-	N_3^-	^-OtBu	MPA^{2-*}	BH_4^-	TU
NH_4^+	71	44	-	80	-	-	-	-	
Li^+	87	60	59	75	74	-	-		
Na^+	77	77	73	71	69	-	-	75	
K^+	66	70	75	90	65	75	58	-	
non-ionic									89

* without 1-PeOH

Table 1b. Measured average temperatures at the outer surface of jar at the end of BM (after 60 min, rounded)

M\X	F^-	Cl^-	Br^-	I^-	N_3^-	$tBuO^-$	MPA^{2-*}	BH_4^-	TU
NH_4^+	40	40	-	43	-	-	-	-	
Li^+	44	41	44	43	41	-	-	-	
Na+	43	41	43	41	40	-	-	41	

K+	41	40	38	44	41	42	41	-
non-ionic								42

* without 1-PeOH

Conversions were calculated from the HPLC chromatograms using UV detection at 210 nm. Although detection was carried out at multiple wavelengths (210 nm, 227 nm, and 260 nm) and using ELSD, the calibration ELSD curves were non-linear for all studied components; TsβCD, p-toluenesulfonic acid (TsOH), and β-CD. The correlation coefficients for all compounds were quite good ($r^2 > 0.99$), however UV detection at 210 nm was used to keep the calculation method consistent because of the large TsβCD concentration differences in samples for TsβCD concentration determination and the fact that the 6^I-monodeoxy-6^I-monofluoro-β-CD compound overlaps with the TsβCD signal. Ts group UV concentration curves were linear across the whole study range and also gave good correlation coefficients ($r^2 > 0.99$ for both TsβCD and TsOH at all used wavelengths). However, the reaction mixture chromatograms were usually very noisy and became useless at higher wavelengths. The TsOH signal was also very noisy in the diluted reaction samples. It was assumed that this was because of EtOH and various salt content in the samples, and so only the TsβCD signals were used in the calculation of the conversion. The products were well separated under the applied HPLC conditions (see Supplementary Information), except 6^I-monodeoxy-6^I-monofluoro-β-CD). The salt peaks overlapped with unsubstituted β-CD in ELSD detection and the chromatograms were often slightly distorted also by the alcohol content of the solution. The pre-work-up determination of formed β-CD also usually failed because of the salt contents of the samples. After work-up, we observed some unreasonable differences between the HPLC chromatograms and the reaction mixture. These conflicts are assumed to not only be due to the known decomposition of the β-CD halogenides and tosylates, but also to the incomplete loss

of poorly soluble β-CD and TsβCD in pure water during work-up and the salt complexations of the products. The formation of inorganic salt complexes with unsubstituted β-CD has been observed the literature,[34,35] and an extremely strong sodium tosylate complex was also found in our experiments. These salt complexes distorted the results of the isolated product analysis. On the other hand, the similarly reactive 6-monohalogeno-β-CDs, except the azido and thioderivatives, somehow also decomposed to β-CD and/or $3^{I},6^{I}$-monoanhydro-β-CD during the work-up. These work-up procedure side reactions distorted the analyses and did not allow the correct determination of these byproducts at our reaction scale to occur and so only qualitative comparisons were carried out. Practically no hydrolysis was observed in the TsβCD-KOtBu co-grinding experiments. The reactions of the salts in solution were often accompanied by hydrolysis, thanks to water traces in the solvents and residual TsβCD water. The hydrolysis of starting TsβCD and 6-monohalogenido-β-CD was found to be a very minor side reaction in the solid state reactions. Relative product formation was determined by ELSD AUCs. In case of the fluoride, ELSD AUCs were calculated from the concentrations of TsβCD by UV detection (AUC_{full}-AUC_{calcd}TsβCD), using the calibration curves.

Thiourea. The thioureido derivative is an important intermediate in the synthesis of 6^{I}-monodeoxy-6^{I}-monothio-β-CD because the formed thiuronium salt is stable and crystallizable. The thiuronium method has some inevitable advantages in the preparation of thiol compounds. These include a lack of unpleasant reagents, such as thiolacetate(s) and sodium sulfide, and the absence of disulfide formation during the reaction. Although the thiuronium method for the preparation of thiol derivatives of CDs is known,[36,37] the use of DMF, the large excess of TU, (usually ten molar fold) the high temperature and the long classic synthesis reaction time naturally

result in side reactions, such as the formation of the $3^{I},6^{I}$-anhydroglucopyranose or N,N-dimethylamino unit.

While HEBM did not change 6^{I}-O-monotosyl-β-CD in the absence of other reactants or in the presence of an alkanol when TU was co-grinded with the TsβCD, almost quantitative conversion and product formation were found with a minimal excess, three molar fold, of TU due to the higher nucleophilicity of the sulfur and the formed stable thiuronium salt. The HPLC analysis of reaction mixtures showed minimal decomposition and starting TsβCD, as shown in Figure 3. The recrystallized reaction mixture was identical to a sample that had been previously prepared by NMR.[28]

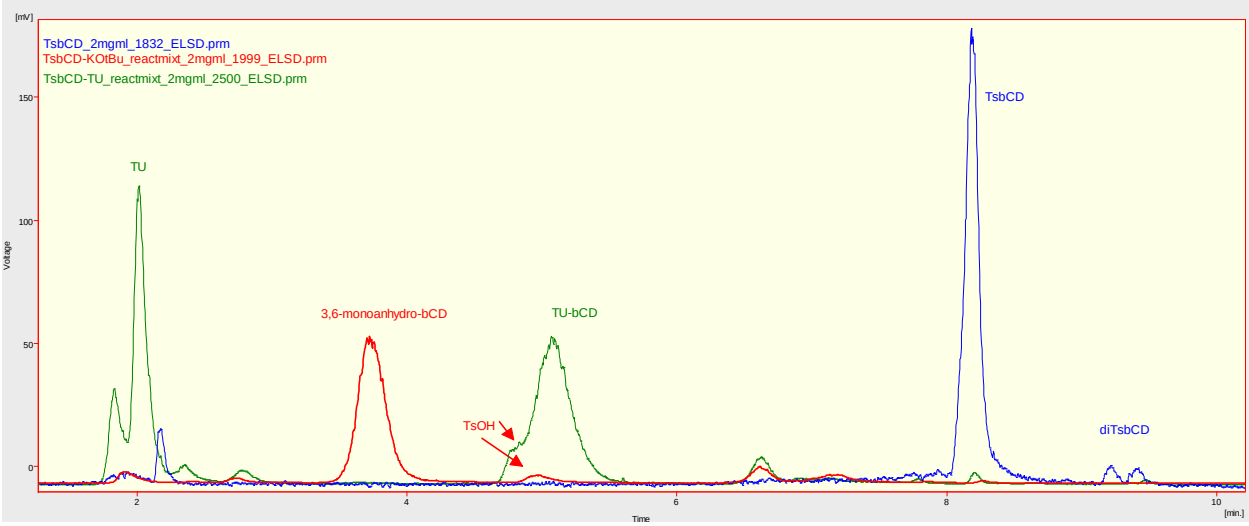


Figure 3. HPLC of reaction mixtures of co-grinded TsβCD-KOtBu and TsβCD-TU mixtures.

Table 2. Conversion of TsβCD during ball milling in the presence of inorganic salts[*,**]

M\X	F^-	Cl^-	Br^-	I^-	N_3^-	$tBuO^-$	MPA^{2-}	BH_4^-	TU	DDS^-
NH_4^+	60	85	-	73	-	-	-	-		-
Li^+	64	76	61	60	91	-	-	-		-

Na+	44	74	73	93	83	-	-	83		-
K+	63	31	88	96	99	97	91	-		92
Not salt									97	

* rounded to integer

** Calculated from chromatograms detected at 210 nm, Calculated TsβCD concentrations are in SI Table S1.

Halogenides. Alkali metal and some ammonium salts were used in these reactions. Although, conversion rates were usually high, as seen in Table 2, product formation was often accompanied by relatively high byproduct contents, particularly in the case of iodide. The baseline separation of the product from TsβCD could not be successfully solved with the fluoride. Preparative chromatography also failed and a strong intermolecular complex between the fluoro- and TsβCD seems to form. The potassium salts gave the highest conversion ratio, as seen in Figure 4,but the reaction, whether substitution or decomposition, was rather more dependent on the anion than the cation, Figure 4 and Figure 7. Substitution efficiency showed poor dependency on Pearson's[39] hardness of cations, with $Li^+ \cong K^+ \cong NH_4^+ > Na^+$ rather than $Li^+ > Na^+ > K^+ > NH_4^+$ observed. However, anion substitution rule[40] was broadly followed as $N_3^- \geq I^- \geq Br^- > Cl^- > F^-$ was found, as can be deduced from Figure 5 and Figure 6. It is worth mentioning that this order is somewhat distorted by the stability of products, which follows the usual N_3»F>Cl>Br>I order.

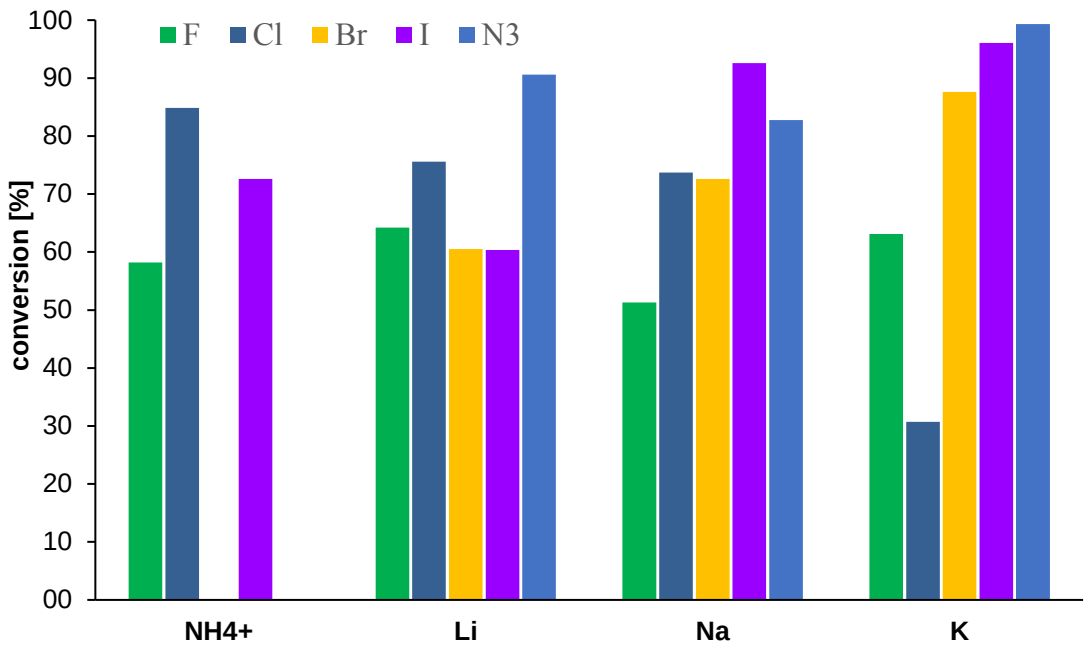


Figure 4. Conversion of TsβCD as a function of cation used.

The effect of the anion on conversion is demonstrated in Figure 5. Bromides, iodides and azides showed increased conversion with increasing ionic sizes, while chlorides showed the opposite tendency.

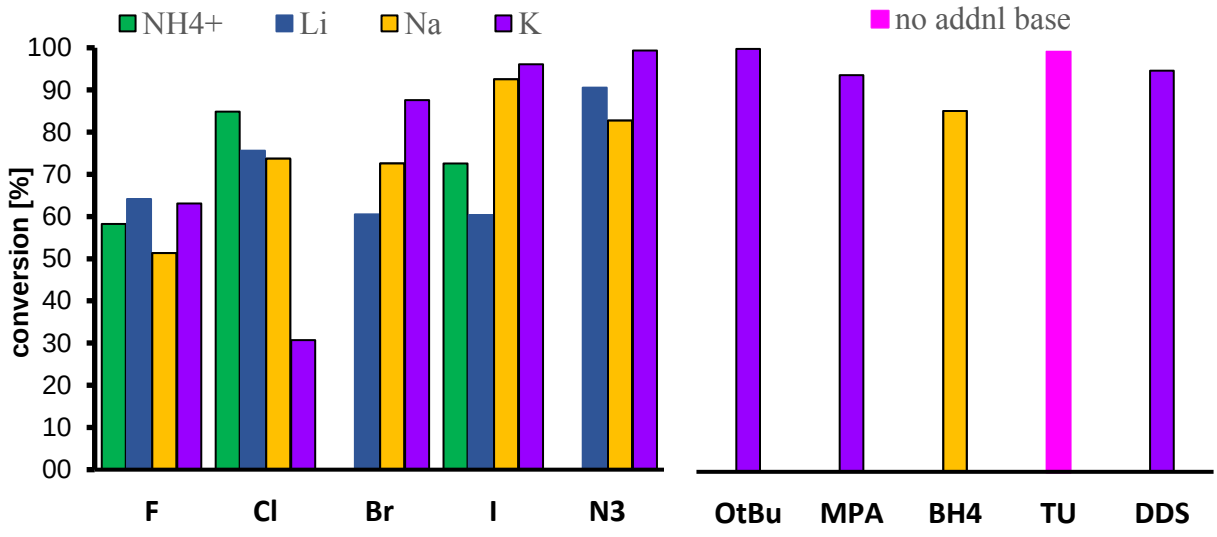


Figure 5. Effect of anions on the conversion of TsβCD in HSBM reactions.

The conversion data alone does not give enough information on the effectiveness of the HSBM reactions. Unfortunately, reaction mixture product content also depends on product stability. The relative product formation ratio, as compared to the potassium salt, showed no real tendencies, as seen in Figure 6 and therefore conclusions from the data are rather qualitative.

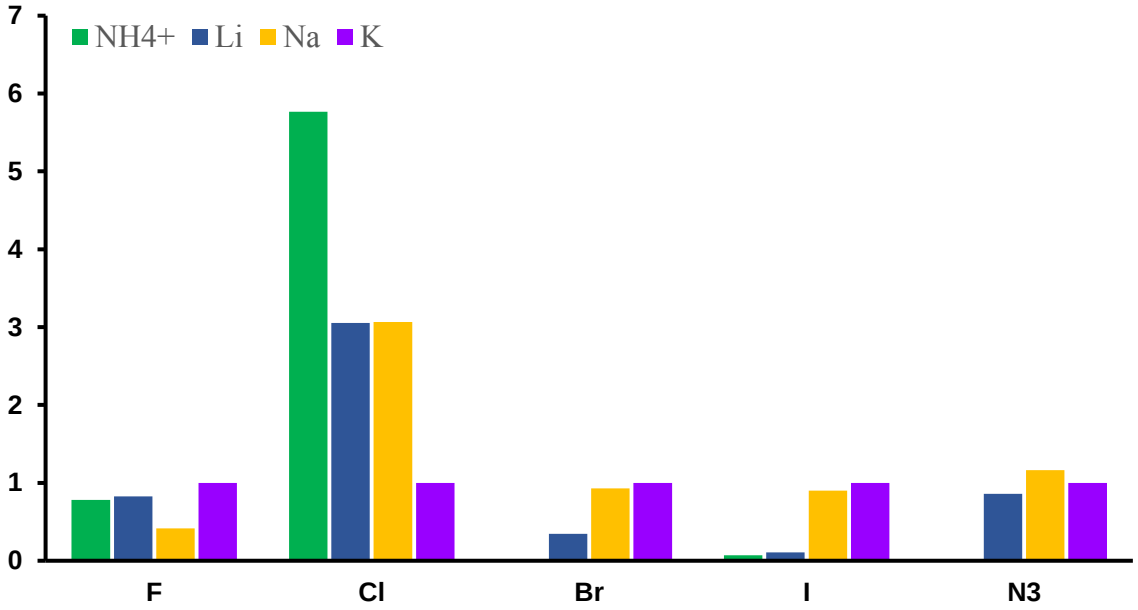


Figure 6. Relative product formation in HSBM reactions (K=1). AUCs of ELSD are in SI Table S2.

The lithium ion showed the highest rate for the anhydratization side reaction, the formation of $3^{I},6^{I}$-monoanhydro-β-CD, as seen in Figure 7, which is in accordance with cation size. Regarding halogen leaving group abilities, it is not surprising that 6-monoiodo-β-CD is the least stable of the studied derivatives, as seen in Figure 8. However, somewhat surprising is the relatively high ratio of $3^{I},6^{I}$-anhydro formation in the azide case, this side reaction is possible only from the starting material, unlike the other test reactions.

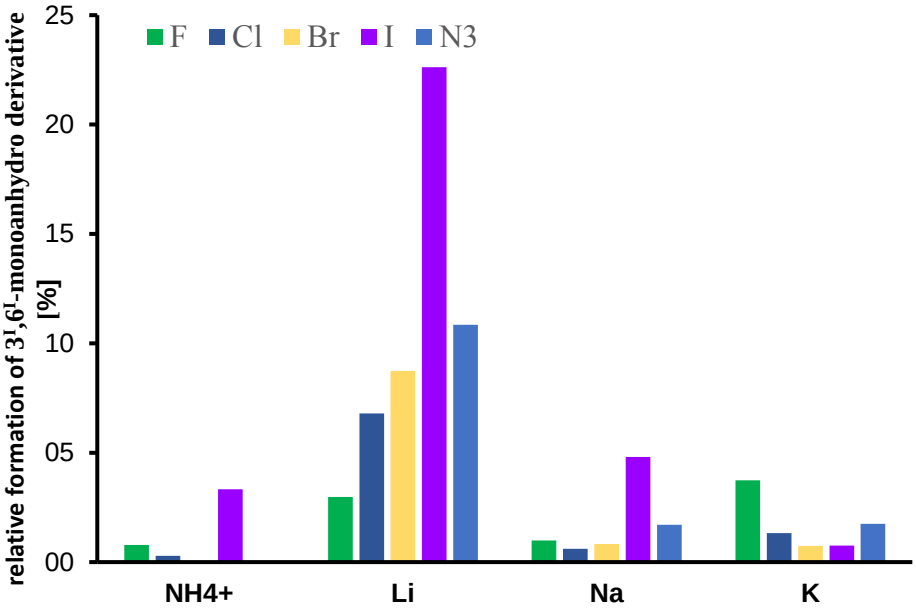


Figure 7. Relative formation ratio of 3,6-monoanhydro-β-CD in the HSBM reactions (KOtBu=100%).

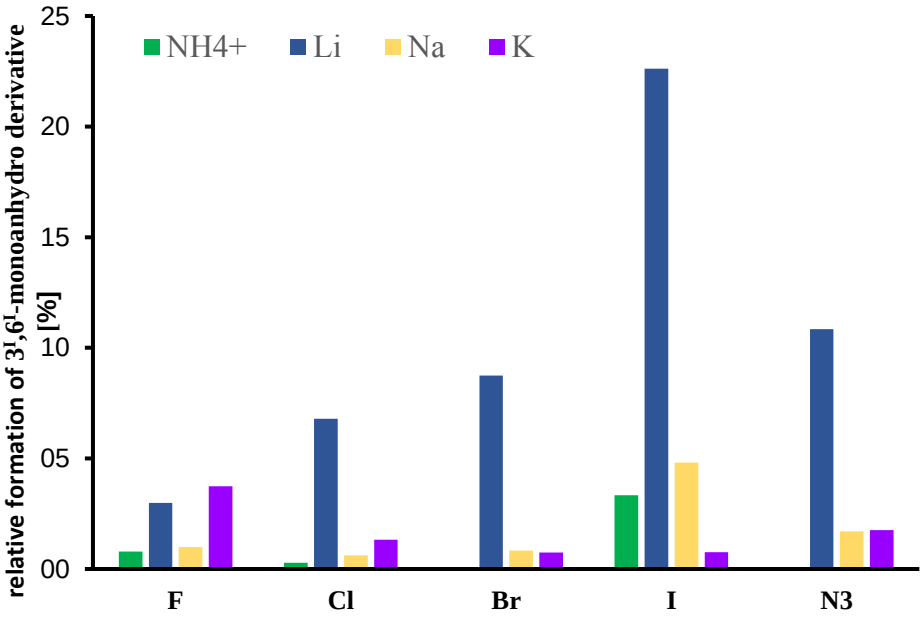


Figure 8. Anion dependency of the formation of 3,6-monoanhydro-β-CD in the HSBM reactions (KOtBu=100%).

Sodium borohydride. Although the hydride anion rarely acts as a nucleophile in complex hydrides, some borohydrides can be used to transfer alkyl halides and p-toluenesulfonate esters of alkanols to alkanes.[41,42] The hydride ion seems to be an obvious nucleophile to use in solid state reactions. It is also true that lithium aluminium hydride may be more appropriate for these transformations, but the presence of both the hydroxyl groups and water traces curb the use of this complex metal hydride. In agreement with common experiences, it was found that, although the conversion rate was moderate as compared to KOtBu, the reagent worked as a strong base rather than a source of the hydride ion.[43] A comparison of the HPLC profile with the KOtBu reaction revealed that the main reaction product is $3^{I},6^{I}$-monoanhydro-β-CD, as seen in Figure 9. A new, very minor product, peak appeared at 7.4 min, which we assume to be 6^{I}-methyl-β-CD.

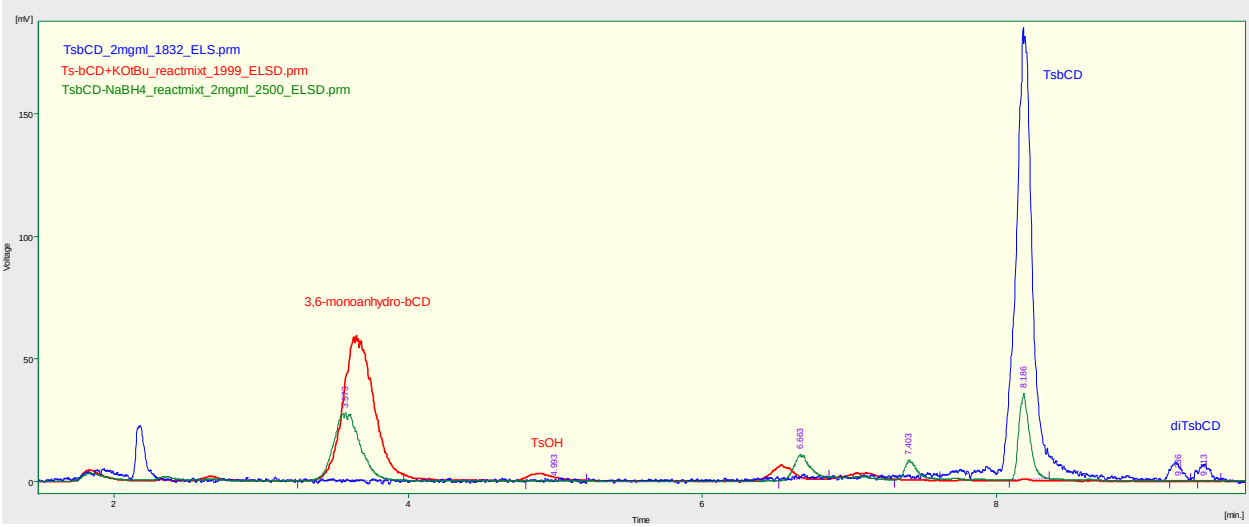


Figure 9. Comparative HPLC of the reaction mixtures of co-grinded TsβCD-KOtBu and TsβCD-$NaBH_4$ mixtures.

Use of additional base. Reaction of thiolates.

Sulfur nucleophiles needed a wetting solvent as the alkali salts of the thiols needed to be prepared in situ because they are unstable and cannot be stored for a long time.

3-Mercaptopropionic acid. Thiolates were prepared *in situ* using KOtBu as the base. Substitution reactions were found to be considerably faster than $3^{I},6^{I}$-monoanhydro product formation. The small mass portions and strong rocky potassium thiolate were difficult to homogenize in the dry method. The addition of 1-PeOH considerably enhanced product formation. It was also found that reaction mixture assembly also affects HSBM reaction outcome. The reaction proceeded moderately without use of a wetting solvent and a considerable amount of the starting thiolate stuck to the bottom of the jar after the reaction. Addition of 1-PeOH to the rocky potassium thiolate did not help. It was found that thiol-1-PeOH-KOtBu-TsβCD and thiol-KOtBu-1-PeOH-TsβCD sequences gave practically identical conversion and product formation results, while the first addition sequence worked slightly but not significantly better. A comparison of reaction mixture HPLC gave poor resolution; however the crude product was well analyzed after work-up, as seen in Figure 10.

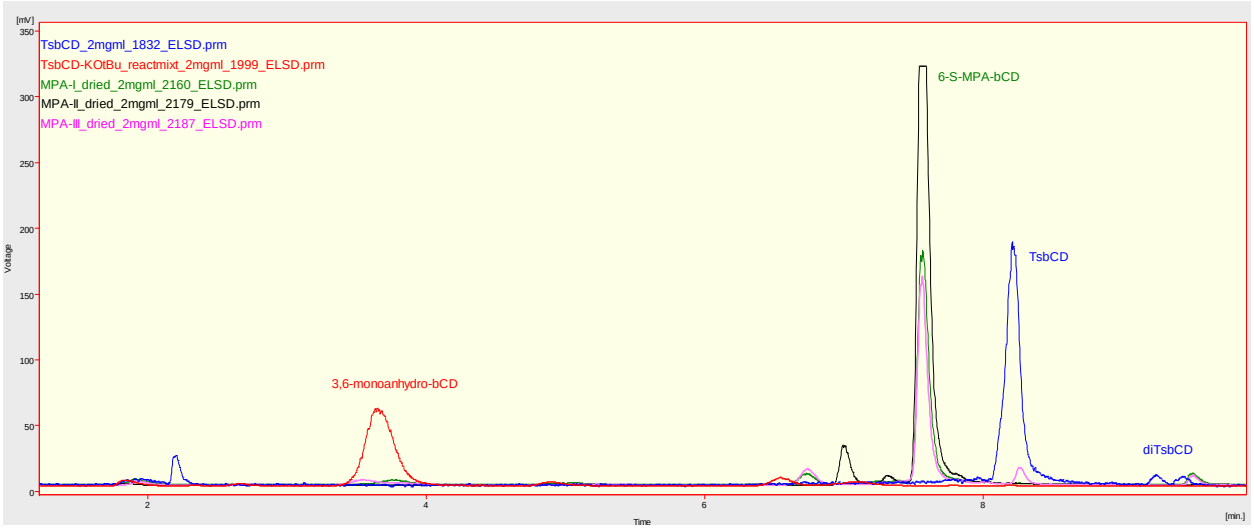


Figure 10. Comparison of MPA reactions. (I: dry conditions; II: MPA-KOtBu-1-PeOH-TsβCD addition order; III: MPA-1-PeOH-KOtBu-TsβCD addition order)

1-Dodecanethiol. The very different solubility profiles for the starting material, product and byproducts in 1-dodecanethiol (DDS) makes isolation quite easy. However, unexpected isolation difficulties were encountered during the isolation and purification processes. The product formed a very strong complex with the starting material and solubilized the otherwise insoluble TsβCD in various organic solvents, such as MeOH and acetone. In these cases, the reaction mixture analysis failed as well. The starting materials and byproducts also affected the chromatogram so much that the quantitative analysis was difficult. Despite the non-baseline HPLC separation, seen in Figure 11, showing that the byproduct level was low, the quantitative analysis gave relatively large calculation errors, preparative separation failed and the isolation of the pure form of the product was not successful. In the case of 1-dodecanethiol, the wet condition reaction assembly gave identical HPLC profiles.

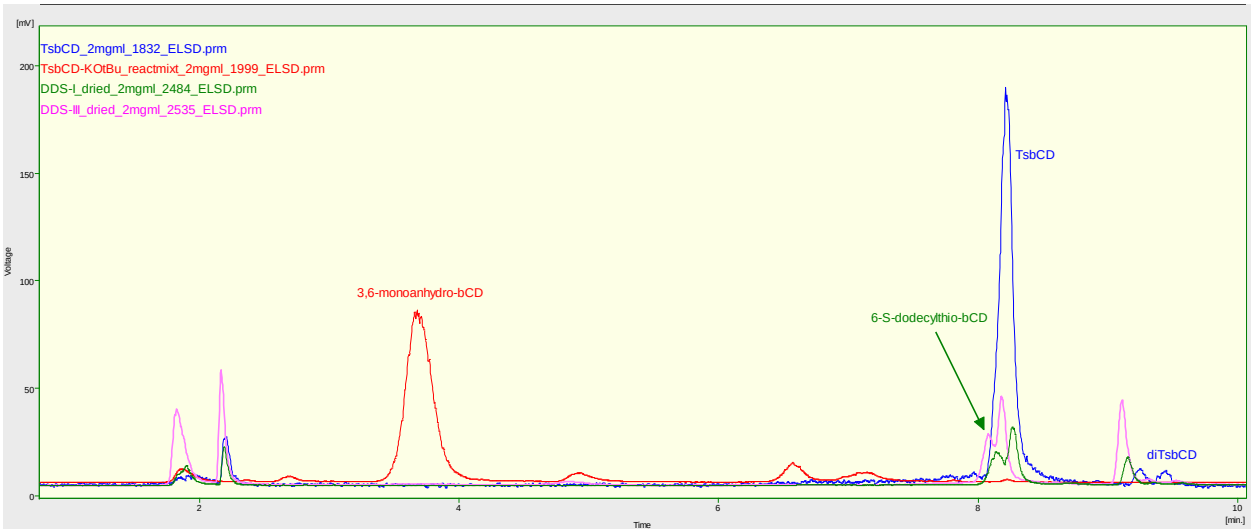


Figure 11. Comparison of dry and wet HSBM methods in the reaction between 1-dodecanethiolate and TsβCD.

Preparative use and scale-up.

6^I-Monoazido-6^I-monodeoxy-β-CD is the most important intermediate in the preparation of 6-monoamino-β-CD derivatives. These single isomer amines are very popular in capillary electrophoretic analysis because of their excellent enantioseparation power. The classic solution preparation yield is rather high, but DMF removal means that isolation and purification are energy-consuming process, while the complete removal of DMF becomes difficult even at a scale of a couple of tens of grams. When only 1-2 grams are necessary, the coproduct of the reaction, sodium tosylate, and the residual sodium azide are difficult to completely remove.[25] The reason for this is that TsONa forms a strong and water soluble complex with the monoazido-β-CD which keeps the otherwise water insoluble product dissolved across a wide concentration range. On a gram scale this difficulty can be solved by using a relatively large amount of organic solvent, such as acetone or MeOH, which might be unreasonable even on 5 gram scale. Both TsONa and NaN_3 can be removed using a very concentrated aqueous solution but it is still necessary to recover the product from the mother liquor. The recrystallized 6^I-monoazido-6^I-monodeoxy-β-CD is practically insoluble in water and if necessary, further recrystallization can be achieved, but gives a poor crystallization yield from water-1-propanol mixtures, for example.

The ball mill reaction of solid materials gives an excellent advantage over classical solvent methods, namely the lack of solvent removal from the reaction mixture. The scale-up of the reaction was realized over two steps; first a twenty five-fold increase in reaction size was performed which was then doubled in the second phase. This latter was the upper limit for the jar used in our experiments, as the low density TsβCD powder did not completely fit the general 1/3 rule of thumb (1/3 volume of reactant and balls fill to ~1/3 volume of the jar). The scalability of the ball milling reaction is good. During the proof of concept, we used a 1:1 ethanol-water mixture for product isolation. Sieving of the product from the balls is more efficient on a larger scale. The

use of the larger jar requires larger balls, but this may mean a solvent is required for crude product isolation to reduce the losses. Comparison of solution and HEBM method is summarized in Table 3.

Table 3. Comparison of classic and HEBM preparation of 6^{I}-monoazido-6^{I}-monodeoxy-β-CD

Method	Scale [mol]	m [g]*	Yield [%]	Max. temperature [°C]	Ball/reagents solvent/reagents
HEBM	0.0001	0.08	69	69 (60 min)	472 (m/m)
Solution	0.0010	0.9	78	100-105	5 (v/m)
HEBM	0.0025	1.6	62	71 (60 min)	482 (m/m)
Solution	0.0030	3.1	89	100-105	5 (v/m)
HEBM	0.0050	5.2	90	71 (60 min) 73 (90 min)	155 (m/m)
Solution	0.0500	57.0	98	100-105	5 (v/m)

* isolated product

In order to reach the maximal outcome from the tosyl-azide exchange further optimization is needed both for the ball milling conditions and in isolation methods of the product. Due to the large number of parameters as pointed in an excellent review of Stolle *et al.*[44] further optimization will reduce the energy impact of the preparative scale synthesis of 6^{I}-monoazido-6^{I}-monodeoxy-β-CD.

CONCLUSIONS

The cation and anion dependencies of Ts exchange have been studied in HEBM reactions. It has been found that the most important intermediary products, the azido and thiuronium derivatives of β-CD, can be efficiently prepared. When no additional reagents were added, the starting key reactant TsβCD remained intact over the whole reaction period. The formation of the 3^{I},6^{I}-

monoanhydro-β-CD is quantitative under co-grinding with a strong base, while the substitution reaction proceed rapidly in the presence of a good nucleophile, such as a sulfide.

While no direct correlation between the cation hardness and anion substitution probability was found, the formation of $3^{I},6^{I}$-monoanhydro-β-CD was the most expressed in the presence of Li^{+}, the hardest of the studied cations.

The scalability of the reaction for the 6^{I}-monoazido-6^{I}-monodeoxy-β-CD was demonstrated as its preparation was increased by up to 50-fold using the same reaction vessel and identical reagent ratios.

Although the hundred milligram scale work-up still requires a relatively large amount of organic solvent, the synthetic procedure completely fulfills green chemistry recommendations. Work is in progress to optimize yields and product purity.

ASSOCIATED CONTENT

Supporting Information. This information is available free of charge via the Internet at http://pubs.acs.org/.

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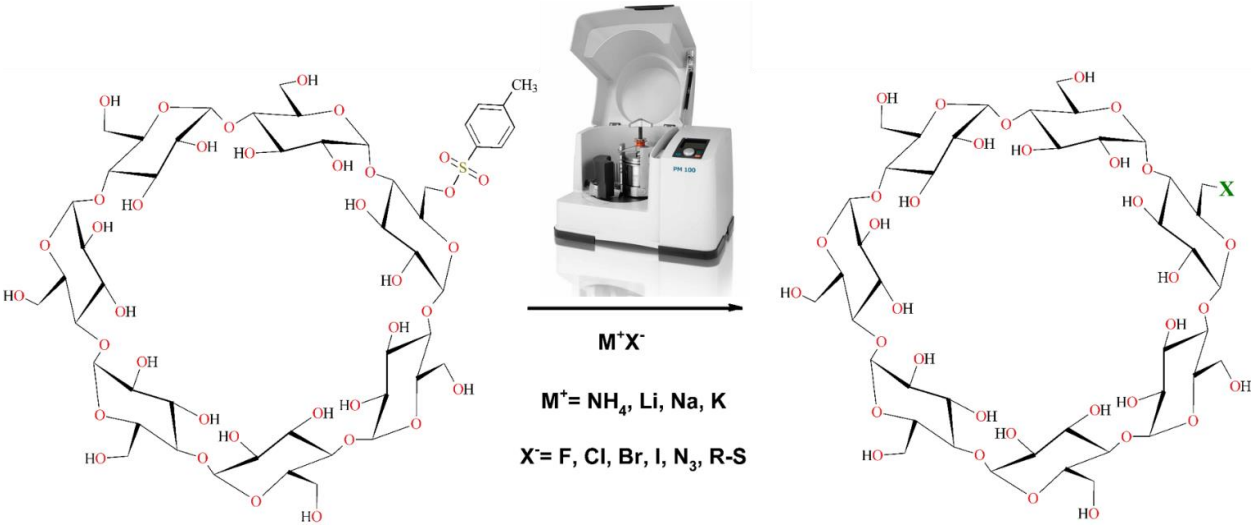
Insert Table of Contents Graphic and Synopsis Here


M+X-
M+= NH4, Li, Na, K
X-= F, Cl, Br, I, N3, R-S
X